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Journal of the Formosan Medical AssociationJournal homepage: <http://www.jfma-online.com>**Perspectives****Resveratrol may be an Effective Prophylactic Agent for Ischemic Stroke**Feng Zhang,¹ Yi Wu^{2*}

Stroke is a leading cause of death and disability that places a heavy burden on society. Effective and reliable treatments are still very limited; therefore, preventive clinical methods are urgently required.

Resveratrol (3,5,4'-trihydroxystilbene) was originally extracted from the roots of white hellebore. Resveratrol was initially classified as a phytoalexin, and it was rediscovered as a cardioprotective agent in 1992. According to epidemiological studies, drinking appropriate amounts of wine, which contains resveratrol, can reduce the morbidity and mortality of coronary heart disease. Moreover, resveratrol decreases myocardial ischemic reperfusion injury in acute and chronic animal models. A series of studies has demonstrated that resveratrol has prophylactic and therapeutic effects for many diseases, including cancer,¹ cardiovascular diseases,² and ischemic injuries.²

However, these studies did not address whether resveratrol could be an effective prophylactic agent for ischemic stroke. Therefore, the potential of resveratrol as a prophylactic medication should be further studied. Hypertension, inflammation,

oxidative stress and diabetes mellitus are significant factors for ischemic stroke; therefore, a method that could alleviate these could be an effective prophylactic intervention for stroke.

First, resveratrol may regulate potent vasodilators such as nitric oxide (NO),³ which could be beneficial for hypertension patients. An experiment in inducible NO synthase (NOS) knockout mice showed that the cardioprotective effect of resveratrol was eliminated, indicating the significant role of NO activation induced by resveratrol.⁴ In summary, vasodilation of NO induced by resveratrol could be beneficial for hypertension patients who have a high risk for ischemic stroke.

Second, Resveratrol can not only inhibit the oxidation of low-density lipoprotein, but also scavenge free radicals.⁵ A recent study has indicated that gavage of 30 mg/kg or 100 mg/kg resveratrol decreased superoxide production and enhanced the inactivation of reactive oxygen species via reversing endothelial NOS uncoupling in mice.⁶

Third, the cyclooxygenase (COX) enzymes play an important role in the generation of proinflammatory molecules, and inhibitors of COX enzymes

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are often used as anti-inflammatory medication. Resveratrol can effectively inhibit COX activity *in vivo* to exert its anti-inflammatory effect. Moreover, resveratrol can dose-dependently inhibit protein kinase C β , connexin 43, transforming growth factor- β 1 and COX-2, and enhance gap junction intercellular communication, suggesting that resveratrol can protect epithelial cells against inflammation.⁷ Therefore, resveratrol can exert its anti-inflammatory effect through the above-mentioned mechanisms.

Fourth, resveratrol (5 mg/kg/day) can effectively decrease the levels of blood glucose, glycosylated hemoglobin, interleukin (IL)-6, tumor necrosis factor- α , NO, IL-1 β and nuclear factor- κ B p65 subunit, to rescue β cells from oxidative injury, without influencing their function and structural integrity.⁸ In addition, resveratrol (10 mg/kg and 20 mg/kg) lowers the level of p65 and I κ B α and alleviates the elevation of tumor necrosis factor- α , IL-6 and COX-2 in diabetic rats. This confirms the nuclear factor- κ B inhibitory and anti-inflammatory role of resveratrol, which can lead to neuroprotection in diabetic neuropathy, except for its antioxidant effect.⁹ Resveratrol could alleviate the symptoms and complications caused by diabetes, to prevent ischemic stroke in patients with diabetes.

With regard to the clinical application of resveratrol, in a multiple-dose study, 40 volunteers received one dose of 25 mg, 50 mg, 100 mg or 150 mg resveratrol, or placebo, and showed no adverse effects. Furthermore, repeated administration of resveratrol was well-tolerated, indicating that resveratrol is safe in clinical practice.¹⁰

In summary, resveratrol could exert neuroprotective activity against ischemic stroke, and alleviate the risk factors for stroke by activating

multiple signaling pathways. Therefore, we speculate that resveratrol might be an effective and reliable agent against ischemic stroke.

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